REMARKS

Claims 1-3, 7-8, 12, and 15-16 are active in this application. Favorable reconsideration is respectfully requested.

The present invention relates to a method for the treatment of brain edema, comprising administering an effective amount of a composition comprising melatonin to a subject having brain edema. See Claim 1.

The rejections under 35 U.S.C. §102(b) and §103(a) over WO 97/20555 (WO '555) are respectfully traversed. This reference does not describe or suggest the claimed method.

The Abstract of WO '555 states that the reference describes a method of treating or preventing anoxic or ischemic brain injury. There is no description in this reference of treating brain edema.

That ischemia is a cause of brain edmea is noted, however, the fact that a subject has an ischemic brain injury does not mean that the subject has brain edema, i.e., one can suffer an ischemic brain injury and have brain edema. Similarly, constricted blood vessels in the brain is a cause of headaches, but one with constricted blood vessels does not necessarily have a headache. Accordingly, WO '555 fails to describe the claimed method. Moreover, there is no suggestion in the reference that melatonin can be used to treat brain edema. Therefore, the claims are neither anticipated by or obvious over WO '555. Withdrawal of these grounds of rejection is respectfully requested.

The rejections under 35 U.S.C. §103(a) over Cuzzocrea in view of Guerrero and, optionally, WO 98/21947 (WO '947), and Keller (U.S. 5,891,465), are respectfully traversed. These references fail to suggest the claimed method.

Cuzzocrea describe that melatonin inhibits the inflammatory response in a paw edema model by inhibiting NO production and scavenging peroxynitrite (see the Abstract). This reference fails to describe treating brain edema. In fact, the edema was induced by injecting carrageenan into the paws of rats, not their brains.

Guerrero describe that melatonin prevents increases in neural NO and cyclic GMP production after transient brain ischemia and reperfusion (see the Abstract). The subjects in Guerrero do not have brain edema. In fact, there is no description or discussion regarding brain edema in this reference whatsoever.

Cuzzocrea and Guerrero, taken in combination, fail to suggest the claimed method. Neither reference discusses brain edema in any fashion. The subjects described in Cuzzocrea had edema in their paws, not their brains, and the subjects in Guerrero were not described as having edema at all. There is simply no motivation to use melatonin to treat brain edema from the combination of Cuzzocrea and Guerrero, when each references fails to even mention brain edema.

In addition, one could not predict from Cuzzocrea and Guerrero that suppressing the production of NO would be effective in treating brain edema. Reference 5 (Zhang et al., Neuroport 1993, cited in the Information Disclosure Statement (IDS) submitted herewith) explicitly demonstrates that administering SNP, which is an NO donor, after ischemia improves the size of the infarction and the administration of an NO synthetase inhibitor such as L-NAME after ischemia makes the infarction worse. Reference 6 (Kuluz et al., Stroke, 1993, cited in the IDS submitted herewith) describes that the effect of L-NAME can be observed when that compound is administered before ischemia. On the other hand, reference 7 (Dawson et al., Neurosci. Lett, cited in the IDS submitted herewith) reports that the administration of L-NAME before and after ischemia showed no effect.

WO '947 relates to compositions and treatment for nighttime persistent reproductive transition symptoms (see the Abstract). This reference is not related to the use of melatonin to treat brain edema and, therefore, fails to remedy the deficiencies of the references discussed above.

Keller describes compositions and methods of administering nutritional supplements (see the Abstract). This reference is not related to the use of melatonin to treat brain edema and, therefore, fails to remedy the deficiencies of the references discussed above.

Cuzzocrea, Guerrero, WO '947, and Keller, considered in combination, fail to suggest the claimed method. Accordingly, Claims 1-3, 7-8, 12, and 15-16 are not obvious over these references. Withdrawal of these grounds of rejection is respectfully requested.

The obviousness-type double patenting rejection over U.S. 6,075,045 is obviated by the executed Terminal Disclaimer submitted herewith. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Applicants submit that the present application is in condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,

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IN THE CLAIMS

Please cancel Claims 4, 5, 6, and 9-11.

Please amend the following claims as follows. All of the pending claims are reproduced for convenience.

--1. (Amended) A method for the treatment [or prevention] of brain edema, comprising administering an effective amount of a composition comprising melatonin to a subject having brain edema [in need of treatment].

2. (Amended) A method as claimed in claim 1, wherein the composition is a pharmaceutical composition and further comprises a pharmaceutically acceptable carrier..

3. (Amended) A method as claimed in claim 2, wherein melatonin is encapsulated in an encapsulating matrix or a liposome.

7. (Amended) A method as claimed in claim 1, wherein the composition is orally administered.

8. (Amended) A method as claimed in claim 1, wherein the composition is a food composition containing the melatonin and a food.

12. (Amended) A method as claimed in claim 8, wherein the food composition is selected from the group consisting of food, a food stuff and a composition comprising melatonin and an additive for incorporating melatonin in food.

Claims 15-16 (New)--